

This Page Is Inserted by IFW Operations  
and is not a part of the Official Record

---

## **BEST AVAILABLE IMAGES**

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

**IMAGES ARE BEST AVAILABLE COPY.**

**As rescanning documents *will not* correct images,  
please do not report the images to the  
Image Problems Mailbox.**

**THIS PAGE BLANK (USPTO)**



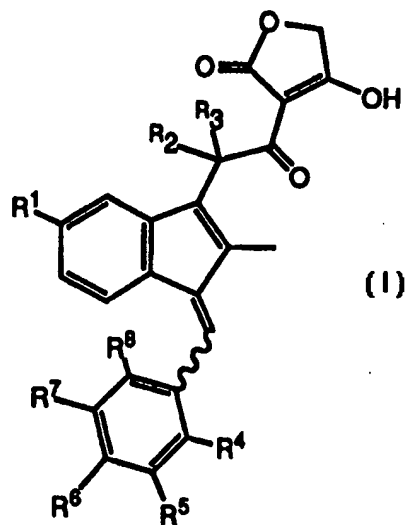
## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification <sup>6</sup> : <b>C07D 307/60, A61K 31/34</b>		<b>A1</b>	(11) International Publication Number: <b>WO 98/21195</b>
			(43) International Publication Date: 22 May 1998 (22.05.98)
(21) International Application Number: PCT/US97/20231			(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).
(22) International Filing Date: 10 November 1997 (10.11.97)			
(30) Priority Data: 08/747,948 12 November 1996 (12.11.96) US			
(71) Applicant: AMERICAN HOME PRODUCTS CORPORATION [US/US]; Five Giralda Farms, Madison, NJ 07940-0874 (US).			
(72) Inventor: FAILLI, Amedeo, Arturo; 14 Landing Lane, Princeton Junction, NJ 08550 (US).			
(74) Agents: ALICE, Ronald, W.; American Home Products Corporation, Patent Law Dept. - 2B, One Campus Drive, Parsippany, NJ 07054 (US) et al.			Published With international search report.

(54) Title: INDENE INHIBITORS OF COX-2

## (57) Abstract

This invention provides compounds of formula (I) having structure (I) wherein: R<sup>1</sup> is hydrogen, halogen, alkyl, alkoxy, fluoroalkoxy, trifluoromethyl, alkylthio, or SCF<sub>3</sub>; R<sup>2</sup> and R<sup>3</sup> are each independently hydrogen or alkyl, or R<sup>2</sup> and R<sup>3</sup> may be taken together to form a saturated cycloalkyl ring; and R<sup>4</sup>, R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup> and R<sup>8</sup> are each independently hydrogen, alkyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, halogen, fluoroalkoxy, CF<sub>3</sub> or SCF<sub>3</sub> which are useful in the treatment of arthritic disorders, colorectal cancer, and Alzheimer's disease.



**FOR THE PURPOSES OF INFORMATION ONLY**

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav	TM	Turkmenistan
BF	Burkina Faso	GR	Greece		Republic of Macedonia	TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's	NZ	New Zealand		
CM	Cameroon		Republic of Korea	PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

- 1 -

**INDENE INHIBITORS OF COX-2****FIELD OF THE INVENTION**

5           This invention is in the fields of antiinflammatory and anticancer pharmaceutical agents and specifically relates to compounds, compositions and methods for treating inflammation and inflammation-associated disorders, such as arthritis and Alzheimer disease, and for the treatment and/or prevention of cyclooxygenase-mediated disorders such as may occur in diabetic retinopathy and tumor angiogenesis. More particularly,  
10       they may prove useful in certain types of cancer growth, such as colorectal cancer and in the treatment of Alzheimer disease.

**BACKGROUND OF THE INVENTION**

15           Prostaglandins have been known for some time to play a major role in the inflammation process, and have been shown to be involved in the pathophysiology of several chronic human diseases. They are involved as mediators of pain, edema and vascular permeability in arthritic diseases such as rheumatoid arthritis and osteoarthritis (Lewis and Kreft, *Immunopharmacol. Immunotoxicol.* **17**, 607-663 (1995)). In  
20       addition, prostaglandins have been postulated to be involved in the pathophysiology of colorectal cancer (Marcus, *New Eng. J. Med.* , **333**, 656-657 (1995); Huang and Heimbrook, *Exp.Opin. Invest. Drugs.*, **4** (3), 243-249 (1995)). Thus an agent that inhibits prostaglandin synthesis may be useful in treating these disorders.

25           The biosynthesis of prostaglandins was previously thought to be due to the action of a single cyclooxygenase enzyme on arachidonic acid to afford prostaglandin H<sub>2</sub> (Vane et al, *Postgrad. Med. J.* , **66** (Suppl 4), S2-S17 (1990); Lewis and Kreft, *Immunopharmacol. Immunotoxicol.* **17**, 607-663 (1995)). This intermediate is subsequently transformed into the various members of the  
30       prostaglandin family by more distal enzymes. The clinical utility of cyclooxygenase inhibitors (often called NSAIDs; nonsteroidal antiinflammatory drugs) is well established in arthritic disorders (Brooks et al, *New Eng. J. Med.* , **324**, 1716-1725 (1991)). However, these compounds also affect other prostaglandin-regulated processes not associated with inflammation but rather, with maintenance of  
35       gastrointestinal integrity and renal blood flow (Dajani et al. *J. Physiol. Pharmacol.*, **46**, 3-16 (1995); Somasundaram et al. *Scand. J. Gastroenterol.*, **30**, 289-299 (1995)), via a mechanism involving inhibition of prostaglandin G/H synthase or cyclooxygenase (COX). Thus, at high doses often necessary to show therapeutic efficacy, most NSAIDs show severe gastric and renal side effects, including life

- 2 -

threatening ulcers that limit their therapeutic utility. An alternative to NSAIDs is the use of corticosteroids, which have even more severe liabilities, especially when long term therapy is involved.

5 Under the old paradigm of a single cyclooxygenase enzyme, it appeared that the selective inhibition of prostaglandin synthesis in inflamed tissue versus inhibition of prostaglandin synthesis in G.I. tissue was unlikely unless tissue specificity could be achieved.

10 Recently, the discovery that there are two distinct cyclooxygenase isozymes in the arachidonic acid/prostaglandin pathway, has given rise to a new paradigm which may lead to compounds that have a separation of inhibition of prostaglandin synthesis in inflamed tissue from inhibition of prostaglandin synthesis in G.I. tissue (Hayllar, *Lancet*, **346**, 521-522 (1995), Lewis and Kreft, *Immunopharmacol. Immunotoxicol.* **17**, 607-663 (1995)). In the new paradigm the constitutive cyclooxygenase enzyme  
15 responsible for prostaglandin synthesis in G.I. tissue is termed COX-1 and the inducible cyclooxygenase enzyme (reported by Hla and Nielson, *Proc. Natl. Acad. Sci. USA*, **89**, 7384 (1992)) responsible for prostaglandin synthesis in inflamed tissue is termed COX-2. COX-1 appears to have a physiological role being involved in maintenance of gastrointestinal integrity and renal blood flow, while COX-2 appears to  
20 be mainly responsible for the pathological effects of prostaglandins.

Several groups have reported that NSAIDs vary in their ability to inhibit COX-1 and COX-2 so that selective inhibition may be possible (O'Neill et al, *Molec. Pharmacol.*, **45**, 245-254 (1994); Laneuville et al, *J. Pharmacol. Exp. Ther.*, **271**, 927-934 (1994); Mitchell et al, *Proc Natl. Acad. Sci. USA*, **90**, 11693-11697  
25 (1993)). The current opinion suggests that a selective inhibitor of COX-2 will have clinical efficacy in inflammatory diseases with reduced potential for gastrointestinal toxicity and renal side effects. There is evidence from animal models to support this hypothesis (Chan et. al *J. Pharmacol. Exp. Ther.* **274**, 1531-1537 (1995); Masferrer et. al. *Proc. Natl. Acad. Sci. USA*, **91**, 3228-3232 (1994); Seibert et al., *Proc. Natl.*  
30 *Acad. Sci. USA*, **91**, 12013-12017 (1994)). Moreover, this may be the mechanism behind the improved G.I. safety of the NSAID etodolac, which has been reported to show a tenfold selectivity for inhibition of COX-2 (Glaser et al. *Eur. J. Pharmacol.* **281**, 107-111 (1995)).

Indomethacin, a relatively non-selective inhibitor of COX-1 and COX-2 has  
35 been shown to be useful in the treatment of Alzheimer's disease (Rogers et al., *Neurology* **43**, 1609-1611 (1993)). These findings suggest that novel COX-2 inhibitors would be attractive targets for the treatment of Alzheimer disease and for

- 3 -

antiarthritic therapy with reduced potential for gastrointestinal toxicity and renal side effects. In addition, the COX-2 enzyme has been shown to be upregulated in colorectal cancer and a selective COX-2 inhibitor may also be of use in this disease (Sano et. al. *Cancer Res.*, 55, 3785-3789 (1995); Huang and Heimbrook, *Exp. Opin. Invest. Drugs* 4 (3), 243-249, (1995)).

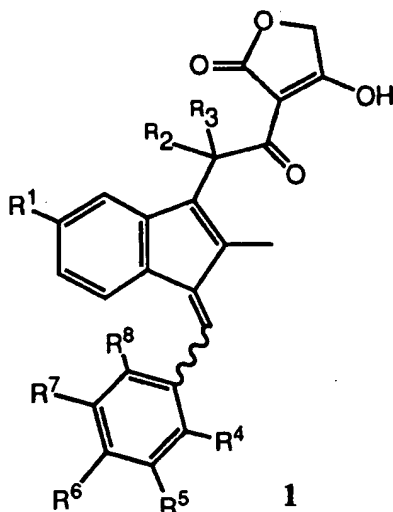
Certain tetronic, thiotetronic and tetramic acid derivatives are described in U.S. Patent 5,420,153 as phospholipase A<sub>2</sub> inhibitors with antiinflammatory properties, and modulators of PAF-mediated biological processes useful as antifertility agents.

Certain substituted indenyl acetic acids are described in U.S. Patents 3,654,349 and 3,647,858 with antiinflammatory, antipyretic and analgesic properties.

The above-cited patents disclose compounds that are structurally different from the compounds of the present invention. In addition, the compounds of the present invention are cyclooxygenase inhibitors, and unexpectedly exhibit marked selectivity for the inhibition of COX-2 over COX-1. The compounds disclosed in each of the patents cited above unlike the compounds of the present invention, do not act as preferential inhibitors of COX-2; thus, they are not expected to exhibit any of the advantages of the compounds of the present invention, i.e. they are not expected to produce a reduced amount of side effects.

## DESCRIPTION OF THE INVENTION

In accordance with this invention, there are provided COX-2 inhibitors which are useful as antiarthritic, anticancer and anti-Alzheimers agents of formula I:



- 4 -

wherein:

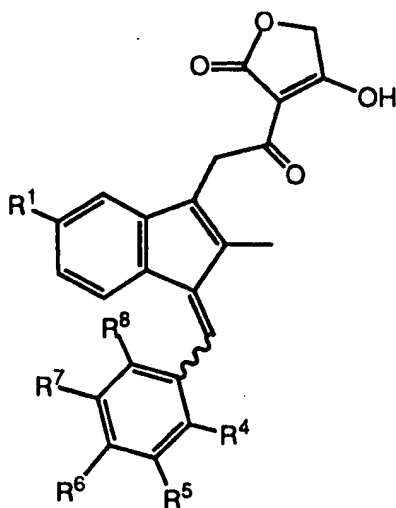
R<sup>1</sup> is hydrogen, halogen, alkyl of 1-6 carbon atoms, alkoxy of 1-6 carbon atoms, fluoroalkoxy of 1-6 carbon atoms, trifluoromethyl, alkylthio of 1-3 carbon atoms, or SCF<sub>3</sub>

5 R<sup>2</sup> and R<sup>3</sup> are each independently, hydrogen or alkyl of 1-6 carbon atoms, or R<sup>2</sup> and R<sup>3</sup> may be taken together to form a saturated cycloalkyl ring of 3-7 carbon atoms; and

10 R<sup>4</sup>, R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup> and R<sup>8</sup> are each independently, hydrogen, halogen, alkyl of 1-6 carbon atoms, alkoxy of 1-6 carbon atoms, alkylthio of 1-3 carbon atoms, alkylsulfinyl of 1-3 carbon atoms, alkylsulfonyl of 1-3 carbon atoms, halogen, fluoroalkoxy of 1-6 carbon atoms, CF<sub>3</sub>, or SCF<sub>3</sub>.

R<sup>1</sup> is preferably lower alkoxy of 1-6 carbon atoms or halogen; R<sup>2</sup> and R<sup>3</sup> are preferably hydrogen; Preferably R<sup>4</sup>, R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup> and R<sup>8</sup> are each independently, 15 hydrogen, halogen, thioalkyl of 1-3 carbon atoms, alkylsulfinyl of 1-3 carbon atoms, alkylsulfonyl of 1-3 carbon atoms, CF<sub>3</sub>, or fluoroalkoxy of 1-6 carbon atoms; more preferably R<sup>4</sup>, R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup> and R<sup>8</sup> are each independently chlorine, hydrogen or thiomethyl. Particular preferred embodiments are those wherein R<sup>7</sup> and R<sup>5</sup> are both 20 hydrogen, more particularly embodiments wherein R<sup>4</sup>, R<sup>6</sup> and R<sup>8</sup> are chlorine or R<sup>4</sup> and R<sup>8</sup> are hydrogen and R<sup>6</sup> is thiomethyl.

Preferred compounds of this invention are those of formula 2:



2

25 wherein

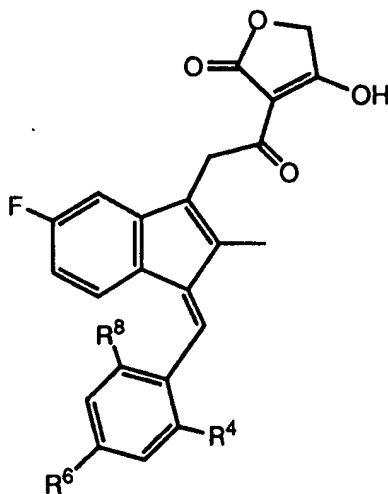
R<sup>1</sup> is lower alkoxy of 1-6 carbon atoms or halogen; and



- 5 -

$R^4$ ,  $R^5$ ,  $R^6$ ,  $R^7$  and  $R^8$  are each independently, hydrogen, halogen, thioalkyl of 1-3 carbon atoms, alkylsulfinyl of 1-3 carbon atoms, alkylsulfonyl of 1-3 carbon atoms,  $CF_3$ , or fluoroalkoxy of 1-6 carbon atoms.

5 More preferred compounds of this invention are those of formula 3:



3

wherein

$R^4$ ,  $R^6$  and  $R^8$  are chlorine; or  $R^4$  and  $R^8$  are hydrogen and  $R^6$  is thiomethyl.

10

Some of the compounds of this invention contain one or more asymmetric centers and may thus give rise to optical isomers and diastereomers. The present invention includes such optical isomers and diastereomers; as well as the racemic and resolved, enantiomerically pure R and S stereoisomers; as well as other mixtures of the R and S stereoisomers. Throughout this application wherever the absolute configuration at the asymmetric center is not indicated, it is intended to embrace both R and S enantiomers as well as mixtures of the two.

15

Certain compounds within the scope of the present invention exist in the form of E and Z stereoisomers and the individual isomers can be differentiated by the prefixes E and Z, as assigned by the accepted sequence rule procedures. Accordingly, the present invention embraces the E, Z and mixed isomer forms of those final product compounds exhibiting this form of stereoisomerism.

20

25 The term alkyl includes both straight chain as well as branched moieties. This includes the alkyl portions of substituents such as alkoxy, thioalkyl, alkylsulfinyl,

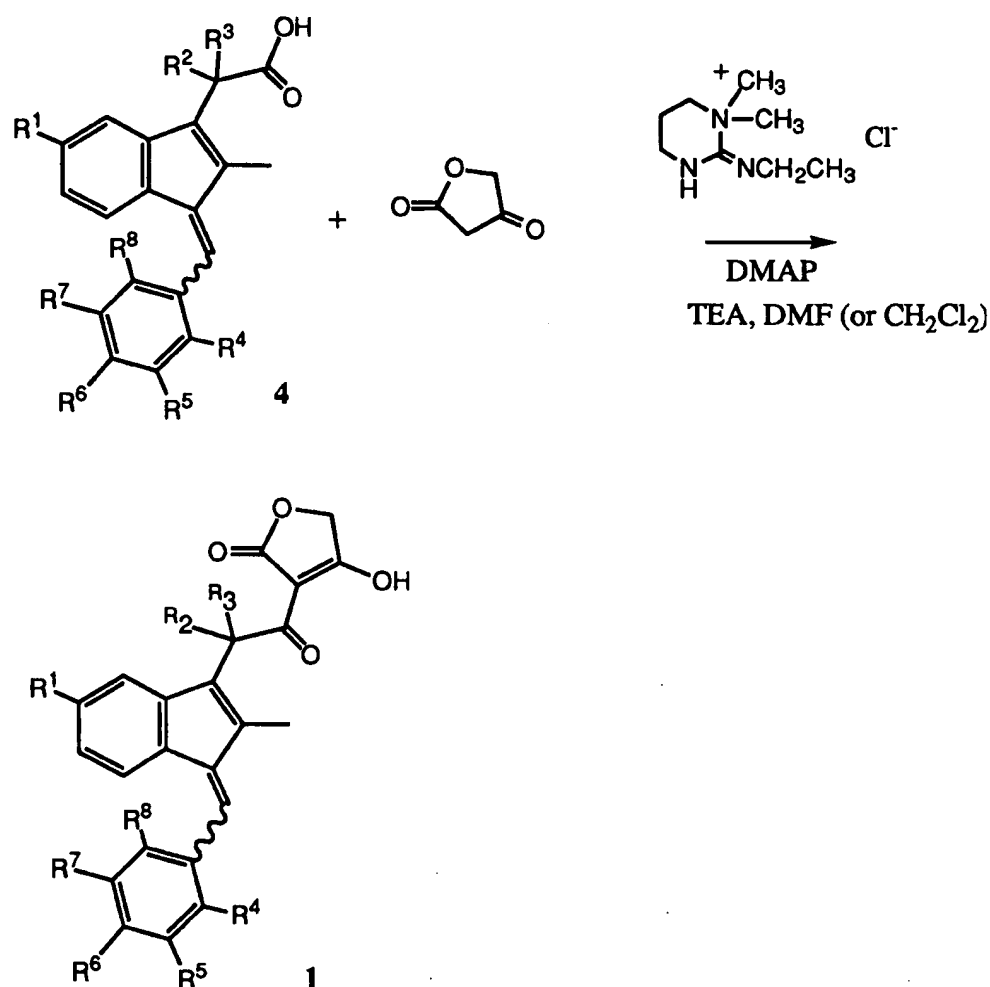
- 6 -

alkylsulfonyl, fluoroalkoxy, and the like. Examples of alkyl include methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, n-pentyl and n-hexyl. The term halo includes fluorine, chlorine, bromine, and iodine. Fluoroalkoxy includes mono-, di-, tri-, and polyfluorinated alkoxy moieties such as -OCF<sub>3</sub>, -OCH<sub>2</sub>F, -OCHF<sub>2</sub>,  
5 -OCH<sub>2</sub>CF<sub>3</sub>, and the like.

The present invention also relates to the use of the compounds described above as a medicament and to their use in the preparation of a medicament for the treatment of arthritic disorders, colorectal cancer or Alzheimer's disease. The invention further  
10 relates to a process for the preparation of the compounds which comprises reacting a substituted indene 3-acetic acid of Formula 4 with a tetronic acid, e.g. as described below.

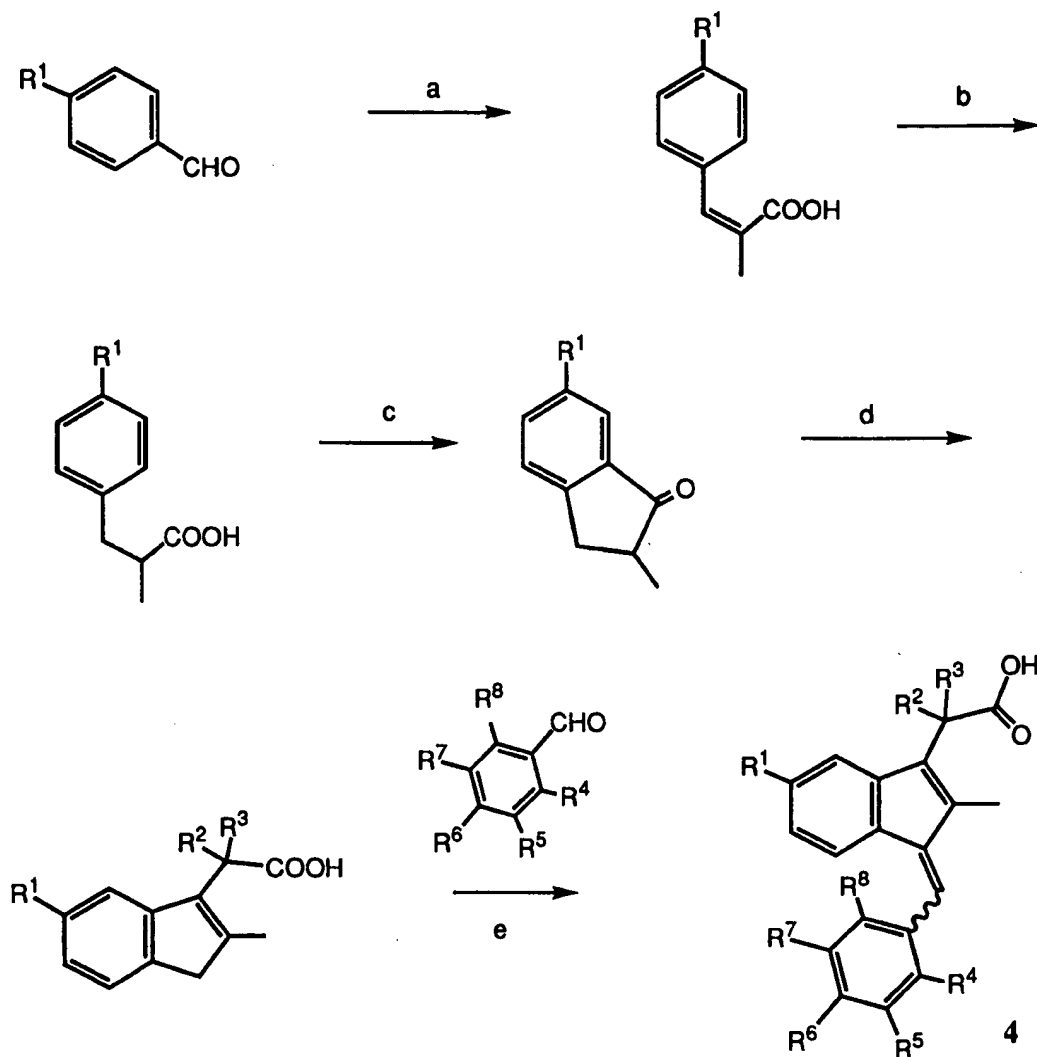
The tetronic acid derivatives of the present invention can be made by a variety of  
15 synthetic routes using conventional methods. According to one preparative scheme (Scheme I) an appropriately substituted indene 3-acetic acid of formula 4 is reacted with a tetronic acid to yield the desired final product of formula 1.

- 7 -

Scheme I

- 5        The substituted indene 3-acetic acids starting materials of formula 4 can be prepared as described in U.S. Patent 3,654,349. A preferred route is shown in Scheme II. Condensation of an appropriately substituted aromatic aldehyde with an acid anhydride and the sodium salt of the same acid provides the corresponding cinnamic acid. The intermediate cinnamic acid is hydrogenated in presence of a
- 10        palladium catalyst to the corresponding hydrocinnamic acid. The intermediate hydrocinnamic acid is cyclized in hot polyphosphoric acid and the resulting indanone is condensed with a cyano acetic acid to provide the substituted indene 3-acetic acid. The intermediate indene 3-acetic acid is then condensed with an appropriately substituted aromatic aldehyde in the presence of an alkoxide to produce the intermediate indenyl
- 15        acetic acid of formula 4.

- 8 -

Scheme II

REAGENTS: (a)  $C_2H_5COOCOC_2H_5$ ,  $C_2H_5COONa$ , heat; basify; acidify; (b)  $H_2$ , 5% Pd-C, EtOH; (c) PPA, heat; (d)  $NC\ C(R^2R^3)\ COOH$ ,  $CH_3COONH_4$ , AcOH, toluene, heat; basify, acidify; (e) MeONa, MeOH; acidify

5

The compounds of the present invention inhibit the COX-2 enzyme (Table 1) believed to be responsible for the production of high levels of prostaglandins in inflammation and certain types of cancer, such as colorectal cancer. It has been shown that preferential inhibition of the COX-2 enzyme relative to COX-1 inhibition leads to an anti inflammatory effect with substantially reduced G.I. toxicity (Chan et al, J.

10

- 9 -

*Pharmacol. Exp. Ther.* **274**, 1531-1537 (1995); Masferrer et al. *Proc. Natl. Acad. Sci. USA*, **91**, 3228-3232 (1994); Seibert et al., *Proc. Natl. Acad. Sci. USA*, **91**, 12013-12017 (1994)). Futaki et al. (*Gen. Pharmac.* **24**, 105-110, 1993) have reported that a selective COX-2 inhibitor N-(2-cyclohexyloxy-4-nitrophenyl)methanesulfonamide is an effective antiinflammatory and lacks gastric side effects. Therefore, the compounds of this invention by virtue of their inhibition of cyclooxygenase-2 and/or their specificity for cyclooxygenase-2 over cyclooxygenase-1, are for the treatment of inflammatory diseases such as rheumatoid arthritis and Alzheimer disease, and of certain types of cancer particularly in patients with peptic ulcers, gastric lesions and other gastric disorders because of their safer profile.

A representative compound of this invention was evaluated for inhibition of COX-2 and COX-1 enzymes as follows. Human COX-1 and COX-2 cDNAs were cloned from human monocytes, untreated and LPS-treated respectively, by RT-PCR using oligonucleotide primers based on published hCOX-1 and hCOX-2 sequences (Jones et al., *J. Biol. Chem.*, **268**, 9049 (1993)). The cDNAs were then transfected into either Sf9 or CHO cells and subsequently converted into a microsomal preparation as described by Glaser et al (*Eur. J. Pharmacol.* **281**, 107-111 (1995)). The microsomal human recombinant enzymes were diluted with buffer (100 mM Tris, pH 7.8 at 37°C) containing 0.5 mM phenol (964 µl total volume). The enzyme preparations were preincubated with vehicle (DMSO) or compounds in DMSO (1% DMSO in final assay) for 30 min at 37°C. Excess hematin was added 1 min prior to initiation of reaction (1.25 µM final hematin) with 30 µM arachidonic acid (sodium salt). Final assay volume was 1.0 ml (100 mM Tris (pH 7.8), 0.5 mM phenol, 1.25 µM hematin and 30 µM arachidonic acid at 37°C).

The reaction was incubated for 35 sec (maximum level of PGH<sub>2</sub> accumulation as determined from time course studies), and terminated by addition of 50-60 µL of SnCl<sub>2</sub> (1 mg/ml) in 0.1 N HCl. PGH<sub>2</sub> is quantitatively converted to PGF<sub>2α</sub> by this reaction (50% efficiency of total conversion). The pH of each tube is adjusted to pH 3.0-3.5 with 1N-NaOH and extracted twice with 1.5 ml of ethyl acetate (75-90% efficiency per extraction). Combined ethyl acetate extracts were dried under N<sub>2</sub>(g) and redissolved in EIA buffer (2.0 ml), and PGF<sub>2α</sub> was quantified by EIA.

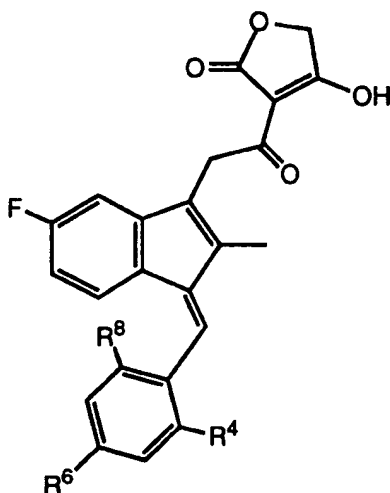
In all cases it has been found that similar results are obtained with either the recombinant human COX-1 or the purified ovine COX-1 enzymes, as reported in the literature (R.A. Copeland et al., *Proc. Natl. Acad. Sci. USA*, **91**, 11202 (1994)). Accordingly, all the COX-1 data reported here are for the purified ovine COX-1 enzyme which was purchased from Cayman Chemicals (Ann Arbor, MI).

- 10 -

The results of the standard pharmacological test procedure described in the preceding paragraphs are shown below.

Table 1. Inhibition of rhCOX-2 and purified ovine COX-1 by indenyl tetronic acids

5



10

Example	$R^4 \quad R^6 \quad R^8$			% inh of rhCOX-2 (IC <sub>50</sub> , $\mu$ M)	% inh of purified ovine COX-1 (IC <sub>50</sub> , $\mu$ M)
	$R^4$	$R^6$	$R^8$		
1	H	SCH <sub>3</sub>	H	(0.027)	100 (10 $\mu$ M)

15

The results in this standard pharmacological test procedures demonstrated high inhibition of the human COX-2 isozyme. Based on the results obtained in this test procedure, the compounds of this invention are useful for the treatment of arthritic disorders, Alzheimer disease and colorectal cancer. The compounds of this invention are also expected to have a high selectivity for the inhibition of the human COX-2 isozyme and would be expected to have a greater margin of G.I. safety in the treatment of arthritic disorders, Alzheimer disease, and colorectal cancer.

25

The compounds of this invention may be administered orally or parenterally, neat or in combination with conventional pharmaceutical carriers. Applicable solid

- 11 -

carriers can include one or more substances which may also act as flavoring agents, lubricants, solubilizers, suspending agents, fillers, glidants, compression aids, binders or tablet-disintegrating agents or an encapsulating material. In powders, the carrier is a finely divided solid which is in admixture with the finely divided active ingredient. In  
5 tablets, the active ingredient is mixed with a carrier having the necessary compression properties in suitable proportions and compacted in the shape and size desired. The powders and tablets, preferably, contain up to 99% of the active ingredient. Suitable solid carriers include, for example, calcium phosphate, magnesium stearate, talc, sugars, lactose, dextrin, starch, gelatin, cellulose, methyl cellulose, sodium  
10 carboxymethyl cellulose, polyvinylpyrrolidone, low melting waxes and ion exchange resins.

Liquid carriers may be used in preparing solutions, suspensions, emulsions, syrups and elixirs. The active ingredient of this invention can be dissolved or  
15 suspended in a pharmaceutically acceptable liquid carrier such as water, an organic solvent, a mixture of both or pharmaceutically acceptable oils or fat. The liquid carrier can contain other suitable pharmaceutical additives such as solubilizers, emulsifiers, buffers, preservatives, sweeteners, flavoring agents, suspending agents, thickening agents, colors, viscosity regulators, stabilizers or osmo-regulators. Suitable examples  
20 of liquid carriers for oral and parenteral administration include water (particularly containing additives as above e.g. cellulose derivatives, preferably sodium carboxymethyl cellulose solution), alcohols (including monohydric alcohols and polyhydric alcohols e.g. glycols) and their derivatives and oils (e.g. fractionated coconut oil and arachis oil). For parenteral administration the carrier can also be an oily  
25 ester such as ethyl oleate and isopropyl myristate. Sterile liquid carriers are used in sterile liquid form compositions for parenteral administration.

Liquid pharmaceutical compositions which are sterile solutions or suspensions can be utilized by, for example, intramuscular, intraperitoneal or subcutaneous  
30 injection. Sterile solutions can also be administered intravenously. Oral administration may be either liquid or solid composition form.

Preferably the pharmaceutical composition is in unit dosage form, e.g. as tablets or capsules. In such form, the composition is sub-divided in unit dose  
35 containing appropriate quantities of the active ingredient; the unit dosage forms can be packaged compositions, for example packeted powders, vials, ampoules, prefilled syringes or sachets containing liquids. The unit dosage form can be, for example, a

- 12 -

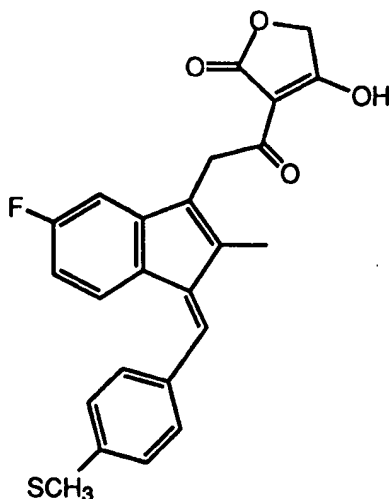
capsule or tablet itself, or it can be the appropriate number of any such compositions in package form.

5 The amount of therapeutically active compound that is administered and the dosage regimen for treating a specific arthritic disorder or colorectal cancer with the compound and/or compositions of this invention depends on a variety of factors, including the weight, age, sex, medical condition of the subject, the severity of the disease, the route and frequency of administration, and the specific compound employed, and thus may vary widely. The pharmaceutical compositions may contain  
10 active ingredient in the range of 0.1 to 2000 mg, preferably in the range of 0.5 to 500 mg and most preferably between 1 and 100 mg. Projected daily dosages of active compound are 0.01 to 100 mg/kg body weight. The daily dose of can be administered in one to four doses per day.

15 The following example illustrate the preparation of a representative compound of this invention.

### Example 1

20 (Z)-3-[ [5-Fluoro-2-methyl-1-[ [4-(methylthio)phenyl]methylene]-1H-inden-3-yl]acetyl]-4-hydroxy-2 (5H)-furanone



25

To a stirred suspension of tetronic acid (0.264 g, 2.64 mmol) in N,N-dimethylformamide (8.5 mL) kept at 0°C was added under a nitrogen atmosphere triethylamine (0.396 mL) followed by 4-dimethylaminopyridine (0.138 mL, 0.974



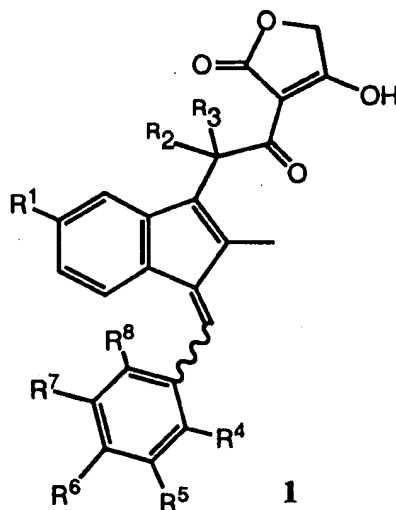
- 13 -

- mmol). The solution was stirred for 5 minutes and 5-fluoro-2-methyl-1-(4-methylthiobenzylidene)-3-acetic acid (1 g, 2.93 mmol; prepared as described in U.S. Patent 3,654,349, which is hereby incorporated by reference) is added at 0°C, followed by 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride (0.607 g, 3.16 mmol). The ice bath was removed and stirring continued overnight at room temperature. Additional triethylamine (0.39 mL) and 4-dimethylamino pyridine (0.138 g) were added and the mixture was stirred for two more days. The solvent was evaporated in vacuo and the residue diluted with water, and acidified to pH 4 with 1N HCl. The precipitated product was collected and the filtrate evaporated to dryness.
- 10 The residue was flash chromatographed (on acid-treated silica Merck-60; eluant: toluene-EtOAc 7:3) to provide additional title compound. This material was combined with the precipitate obtained above and recrystallized from toluene (ethyl acetate)-ether to provide a bright yellow solid (45% yield), m.p. 178-181°C (dec).
- Anal. Calcd. for  $C_{24}H_{19}FO_4S$ : C, 68.23; H, 4.53. Found: C, 68.13; H, 4.37.
- 15 Mass spectrum (+ FAB, m/z): 423  $[M+H]^+$ , 445  $[M+Na]^+$   
IR (KBr): 2920, 1760, 1735, 1650, 1600  $cm^{-1}$   
NMR (400 MHz, DMSO- $d_6$ ):  $\delta$  2.10 (s, 3H,  $CH_3$ ), 2.52 (s, 3H,  $SCH_3$ ), 4.06 (s, 2H,  $CH_2$ ), 4.46 (s, 2H,  $CH_2$ ), 4.2-4.7 (broad signal, exchangeable), 6.68 (m, 1H), 6.92 (m, 1H), 7.23 (s, 1H), 7.30 (m, 1H), 7.35 and 7.49 (m, 4H).

20

## WHAT IS CLAIMED IS:

1. A compound of formula I having the structure
- 5

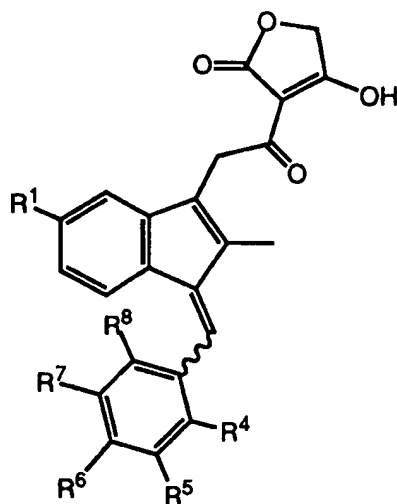


wherein:

- $R^1$  is hydrogen, halogen, alkyl of 1-6 carbon atoms, alkoxy of 1-6 carbon atoms,  
 10 fluoroalkoxy of 1-6 carbon atoms, trifluoromethyl, alkylthio of 1-3 carbon atoms, or  $SCF_3$
- $R^2$  and  $R^3$  are each independently, hydrogen or alkyl of 1-6 carbon atoms, or  $R^2$  and  $R^3$  may be taken together to form a saturated cycloalkyl ring of 3-7 carbon atoms; and
- 15  $R^4$ ,  $R^5$ ,  $R^6$ ,  $R^7$  and  $R^8$  are each independently, hydrogen, alkyl of 1-6 carbon atoms, alkoxy of 1-6 carbon atoms, alkylthio of 1-3 carbon atoms, alkylsulfinyl of 1-3 carbon atoms, alkylsulfonyl of 1-3 carbon atoms, halogen, fluoroalkoxy of 1-6 carbon atoms,  $CF_3$ , or  $SCF_3$ .

- 15 -

2. The compound according to claim 1 of formula 2 having the structure



2

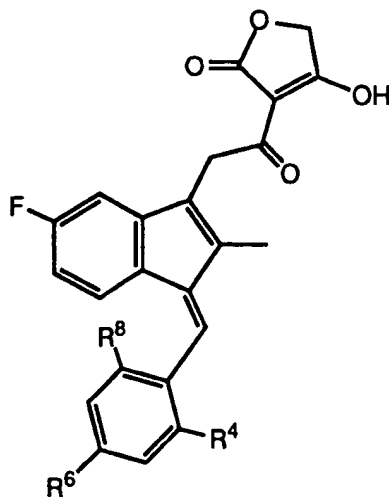
5 wherein

R<sup>1</sup> is lower alkoxy of 1-6 carbon atoms or halogen; and

R<sup>4</sup>, R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup> and R<sup>8</sup> are each independently, hydrogen, halogen, thioalkyl of 1-3 carbon atoms, alkylsulfinyl of 1-3 carbon atoms, alkylsulfonyl of 1-3 carbon atoms, CF<sub>3</sub>, or fluoroalkoxy of 1-6 carbon atoms.

10

3. The compound according to claim 2 of formula 3 having the structure



3

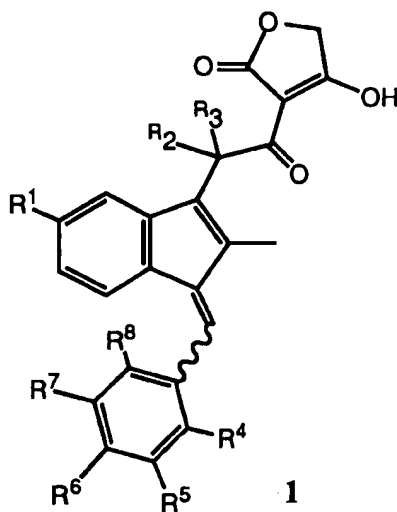
15 wherein

R<sup>4</sup>, R<sup>6</sup> and R<sup>8</sup> are chlorine; or R<sup>4</sup> and R<sup>8</sup> are hydrogen and R<sup>6</sup> is thiomethyl.

- 16 -

4. The compound according to claim 1, which is (Z)-3-[ [5-fluoro-2-methyl-1-[4-(methylthio)phenyl]methylene]-1H-inden-3-yl]acetyl]-4-hydroxy-2 (5H)-furanone.

5. A method of treating arthritic disorders in a mammal in need thereof which comprises administering to said mammal an effective amount of a compound of formula 1 having the structure



10

wherein:

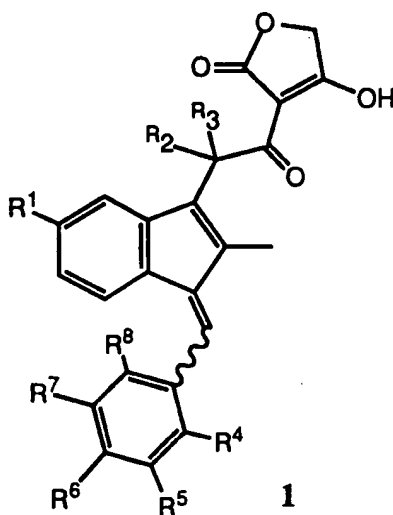
R<sup>1</sup> is hydrogen, halogen, alkyl of 1-6 carbon atoms, alkoxy of 1-6 carbon atoms, fluoroalkoxy of 1-6 carbon atoms, trifluoromethyl, alkylthio of 1-3 carbon atoms, or SCF<sub>3</sub>

- 15 R<sup>2</sup> and R<sup>3</sup> are each independently, hydrogen or alkyl of 1-6 carbon atoms, or R<sup>2</sup> and R<sup>3</sup> may be taken together to form a saturated cycloalkyl ring of 3-7 carbon atoms; and

- R<sup>4</sup>, R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup> and R<sup>8</sup> are each independently, hydrogen, alkyl of 1-6 carbon atoms, alkoxy of 1-6 carbon atoms, alkylthio of 1-3 carbon atoms, alkylsulfinyl of 1-3 carbon atoms, alkylsulfonyl of 1-3 carbon atoms, halogen, fluoroalkoxy of 1-6 carbon atoms, CF<sub>3</sub>, or SCF<sub>3</sub>.
- 20

- 17 -

6. A method of treating colorectal cancer in a mammal in need thereof which comprises administering to said mammal an effective amount of a compound of formula 1 having the structure



5

wherein:

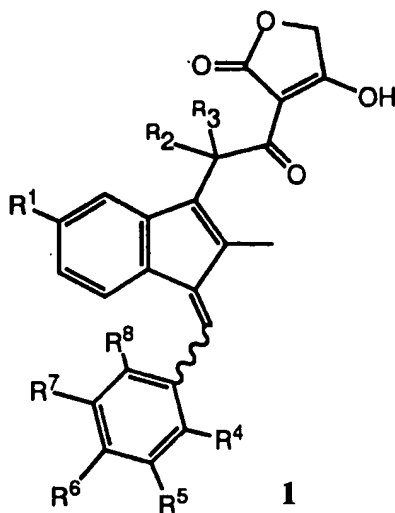
- $R^1$  is hydrogen, halogen, alkyl of 1-6 carbon atoms, alkoxy of 1-6 carbon atoms, fluoroalkoxy of 1-6 carbon atoms, trifluoromethyl, alkylthio of 1-3 carbon atoms, or  $SCF_3$
- $R^2$  and  $R^3$  are each independently, hydrogen or alkyl of 1-6 carbon atoms, or  $R^2$  and  $R^3$  may be taken together to form a saturated cycloalkyl ring of 3-7 carbon atoms; and
- $R^4$ ,  $R^5$ ,  $R^6$ ,  $R^7$  and  $R^8$  are each independently, hydrogen, alkyl of 1-6 carbon atoms, alkoxy of 1-6 carbon atoms, alkylthio of 1-3 carbon atoms, alkylsulfinyl of 1-3 carbon atoms, alkylsulfonyl of 1-3 carbon atoms, halogen, fluoroalkoxy of 1-6 carbon atoms,  $CF_3$ , or  $SCF_3$ .

10

15

- 18 -

7. A method of treating Alzheimer's disease in a mammal in need thereof which comprises administering to said mammal an effective amount of a compound of formula 1 having the structure



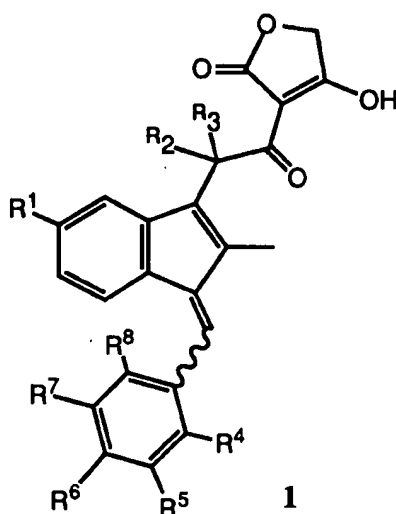
5

wherein:

- 10  $R^1$  is hydrogen, halogen, alkyl of 1-6 carbon atoms, alkoxy of 1-6 carbon atoms, fluoroalkoxy of 1-6 carbon atoms, trifluoromethyl, alkylthio of 1-3 carbon atoms, or  $SCF_3$
- $R^2$  and  $R^3$  are each independently, hydrogen or alkyl of 1-6 carbon atoms, or  $R^2$  and  $R^3$  may be taken together to form a saturated cycloalkyl ring of 3-7 carbon atoms; and
- 15  $R^4$ ,  $R^5$ ,  $R^6$ ,  $R^7$  and  $R^8$  are each independently, hydrogen, alkyl of 1-6 carbon atoms, alkoxy of 1-6 carbon atoms, alkylthio of 1-3 carbon atoms, alkylsulfinyl of 1-3 carbon atoms, alkylsulfonyl of 1-3 carbon atoms, halogen, fluoroalkoxy of 1-6 carbon atoms,  $CF_3$ , or  $SCF_3$ .

- 19 -

8. A pharmaceutical composition which comprises a compound of formula 1 having the structure



5

wherein:

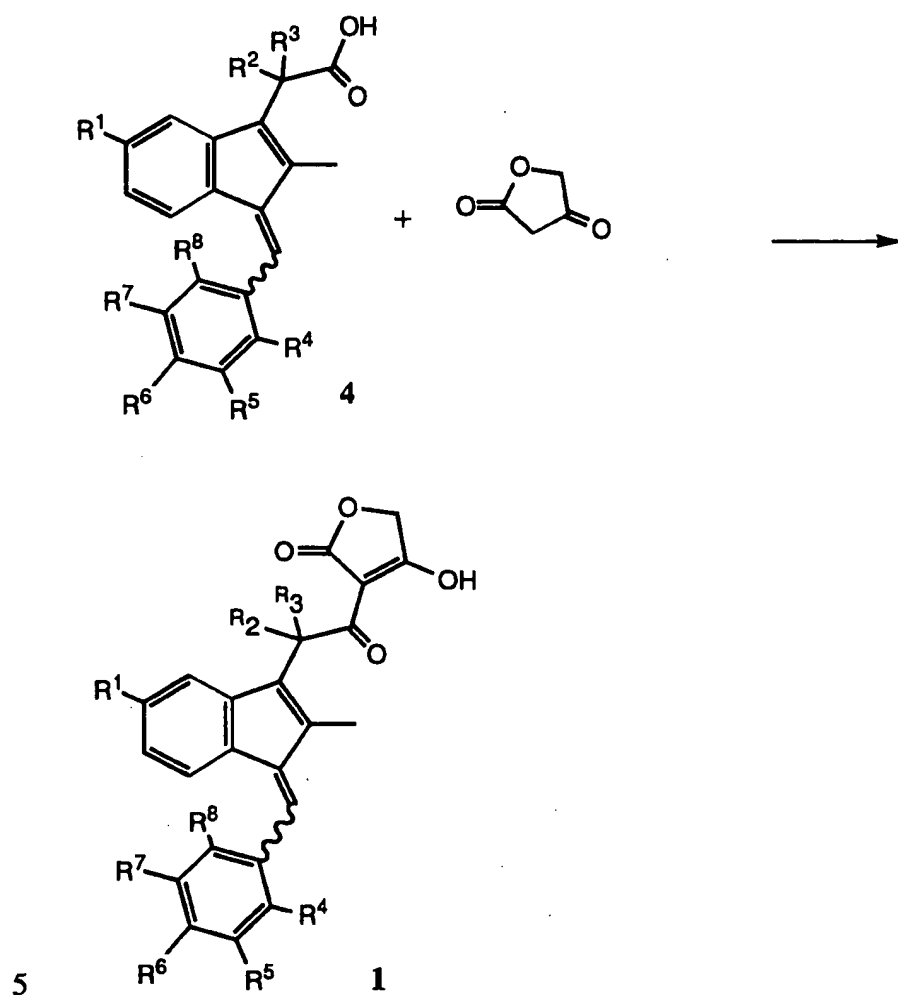
- $R^1$  is hydrogen, halogen, alkyl of 1-6 carbon atoms, alkoxy of 1-6 carbon atoms, fluoroalkoxy of 1-6 carbon atoms, trifluoromethyl, alkylthio of 1-3 carbon atoms, or  $SCF_3$
- 10  $R^2$  and  $R^3$  are each independently, hydrogen or alkyl of 1-6 carbon atoms, or  $R^2$  and  $R^3$  may be taken together to form a saturated cycloalkyl ring of 3-7 carbon atoms; and
- $R^4$ ,  $R^5$ ,  $R^6$ ,  $R^7$  and  $R^8$  are each independently, hydrogen, alkyl of 1-6 carbon atoms, alkoxy of 1-6 carbon atoms, alkylthio of 1-3 carbon atoms, alkylsulfinyl of 1-3 carbon atoms, alkylsulfonyl of 1-3 carbon atoms, halogen, fluoroalkoxy of 1-6 carbon atoms,  $CF_3$ , or  $SCF_3$  and a pharmaceutical carrier.
- 15

9. Use of a compound as claimed in any one of Claims 1 to 4 as a medicament.

- 20 10. Use of a compound as claimed in any one of Claims 1 to 4 in the preparation of a medicament for the treatment of arthritic disorders, colorectal cancer or Alzheimer's disease.

- 20 -

11. A process for the preparation of a compound as claimed in any one of Claims 1 to 4 comprising reacting a substituted indene 3-acetic acid of Formula 4 with a tetronic acid:





## INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 97/20231

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D307/60 A61K31/34

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 675 103 A (SCOTIA HOLDINGS PLC) 4 October 1995 see page 6, line 14 - line 25; claims ---	1-11
A	US 5 420 153 A (SCHIEHSE GUY A ET AL) 30 May 1995 cited in the application see abstract; claims ---	1-11
A	US 3 647 858 A (HINKLEY DAVID F ET AL) 7 March 1972 cited in the application see page -; claims -----	1-11



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

## \* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&amp;" document member of the same patent family

Date of the actual completion of the international search

17 February 1998

Date of mailing of the international search report

05.03.98

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+31-70) 340-3016

Authorized officer

Paisdor, B

# INTERNATIONAL SEARCH REPORT

national application No.

PCT/US 97/20231

## Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 5-7  
because they relate to subject matter not required to be searched by this Authority, namely:  
Remark: Although claim(s) 5-7  
is(are) directed to a method of treatment of the human/animal  
body, the search has been carried out and based on the alleged  
effects of the compound/composition.
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such  
an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all  
searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment  
of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report  
covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is  
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 97/20231

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0675103 A	04-10-95	AU 1348095 A CA 2143604 A CN 1117484 A FI 950910 A JP 7304688 A NO 950785 A NZ 270589 A SG 28202 A US 5603959 A ZA 9501661 A	07-09-95 02-09-95 28-02-96 02-09-95 21-11-95 04-09-95 24-06-97 01-04-96 18-02-97 08-12-95
US 5420153 A	30-05-95	US 5366993 A US 5468774 A AU 4118193 A MX 9302419 A WO 9322305 A	22-11-94 21-11-95 29-11-93 31-03-94 11-11-93
US 3647858 A	07-03-72	NONE	

**THIS PAGE BLANK (USPTO)**